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**REMARKS**

Claims 1-4, 6-9, 11, 12, 14 and 15 are pending in the application. Claims 1-4, 6-9 and 11 are rejected.

**Rejection Under 35 U.S.C. §103(a)**

The rejection of claims 1-4, 6-9 and 11 under 35 U.S.C. §103(a) over Kuo in view of Masure have been maintained. Once again the Examiner states, *inter alia*:

*It would be prima facie obvious at the time the invention was made to add the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pneumolysin conjugate vaccines as taught by Kuo et al because Masure et al teach that one may administer the CBP vaccines in conjunction with one or more pharmaceutical compositions used for treating bacterial infection including but not limited to antibiotics, soluble carbohydrate inhibitors of bacterial adhesion, other small molecule inhibitors of bacterial metabolism, transport or transformation, stimulators of bacterial lysis or antibacterial antibodies or vaccines directed at other bacterial antigens (column 30, lines 34-42). It would be expected barring evidence to the contrary, that the addition of the CBP vaccines of Masure et al to the pneumococcal polysaccharide recombinant pneumolysin polysaccharide recombinant pneumolysin conjugate vaccines as taught by Kuo et al would be effective in treating Streptococcus pneumoniae infections.....*

*It should be noted that the Masure et al teach that the choline binding proteins or fragments thereof mediated adhesion. One of ordinary skill in the art would be motivated to add choline binding proteins or fragments thereof to other vaccine components to prevent bacteria from adhering to the cell surface, thereby preventing infection. If a bacterium cannot adhere to the cell surface then infection is minimized. One of ordinary skill ...*

As stated in response to earlier office action, the point to be emphasized is, arguably it may superficially appear that if one mixes all known antigens and adjuvants available against a disease one might be led to believe one could achieve an improved product. However, vaccine manufacturers and skilled people in the vaccine field live in the real world. Adding components to a vaccine is extremely costly from a price of bulk, clinical trial, quality control, and general complexity point of view. Furthermore, it is known in the art that the more complex a vaccine is the more immune interference can be an issue between components resulting in a worse product. Also more components in a vaccine can lead to greater risk of reactogenicity problems. Thus, a skilled person would not think to add all known available antigens together to achieve an improved vaccine, unless there was an expectation of added value in so doing.

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The Examiner appear to argue that the motivation in combining Kuo and Masure is that one would always combine vaccines shown to be protective. However, Applicant reiterates that the Examiner is using hind-sight reconstruction because, absent the teaching of the present patent application, a skilled person would never have combined the teaching of Kuo and Masure to confer a value added benefit that would overcome the feeling of potential risk of product complexity that the skilled person would have had. Nothing in Kuo and Masure talks about compatibility of each invention with the other, nothing is said about the value added technical advantages that could be realized by the combination. Why would a skilled person combine two unconnected teachings of vaccines which are already said to work well enough by themselves only to increase cost and product risk/complexity when there is absolutely no reason given in the art to do so?

As Applicant submitted in the earlier argument that obviousness test should never be a reconstruction based on hind-sight. In order to establish obviousness there must be a substantial motivating reason for a skilled person to combine teachings with a reasonable expectation of success. Applicant has shown that (1) motivating reason does not provide such a reasonable expectation of success in combining Kuo and Masure. Likewise (2) - proteins that mediate adhesion are POSSIBLE antigen candidates for all bacteria - yet they are not NECESSARY components for an effective vaccine. Again short of a value added reason that such proteins of Masure would positively interact with the polysaccharide of Kuo, there would not be any reasonable expectation of success in combining the teachings taking into account the aversion to the risk a skilled person would have had in combining.

Importantly moreover, in addition to combining Kuo and Masure a skilled person would also have had to select a Th1 adjuvant from all the different types of adjuvant discussed in Kuo. Contrary to the Examiner's argument there is nothing in Kuo to state that Th1 adjuvants are effective in pneumococcal vaccine compositions. Kuo states that Th1 adjuvants could be used as well as Th2 adjuvants - but in the Examples only aluminium phosphate (a Th2 adjuvant) was used (Examples 9 and 12). There is no preference for Th1 adjuvants taught in Kuo - if anything there is a preference for Th2 adjuvants. So what would motivate a skilled person to decide not only that combining the antigens of Kuo and Masure would give a value added effect that would overcome their natural prejudice to vaccine complexity, and furthermore that of all the possible adjuvants a Th1 adjuvant should also be selected? Thus, there was no motivation to connect all these elements - and to do so can only be supported with the knowledge of the present specification.

To elaborate more on this point, Applicant states on page 9, lines 6 – 14, of the present application:

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*"Surprisingly, the present inventors have found that by simultaneously stimulating the cell mediated branch of the immune system (for instance T-cell mediated immunity) in addition to the humoral branch of the immune system (B-cell mediated), a synergy (or cooperation) results which is capable of enhancing the clearance of pneumococci from the host. This is a discovery which will aid the prevention (or treatment) of pneumococcal infection in general, but will be particularly important for the prevention (or treatment) of pneumonia in the elderly where polysaccharide based vaccines do not show efficacy."*

The present inventors have found that both arms of the immune system may synergize in this way if a pneumococcal polysaccharide (preferably conjugated) is administered with a pneumococcal protein (preferably a protein expressed on the surface of pneumococci, or secreted or released, which can be processed and presented in the context of Class II and MHC class I on the surface of infected mammalian cells). Although a pneumococcal protein can trigger cell mediated immunity by itself, the inventors have also found that the presence of a Th1 inducing adjuvant in the vaccine formulation helps this arm of the immune system, and surprisingly further enhances the synergy between both arms of the immune system."

This is further supported by the Examples (see for instance Examples 4 and 5 in the specification) where this cooperation is shown for a particular combination of antigens. This is the type of value added effect that a skilled person would understand as making it worthwhile to combine pneumococcal polysaccharide conjugates, protein antigens and a Th1 adjuvant. With such a technical advantage, the natural caution of the skilled person would be overcome.

Neither Kuo et al. nor Masure et al. discuss such advantages of combining pneumococcal polysaccharide conjugates with proteins and Th1 adjuvant to achieve the above advantages. In conclusion, it is respectfully submitted that the present invention is therefore certainly not obvious over the cited prior art.

#### **Rejection Under 35 U.S.C. §112, First Paragraph**

Claims 1-4, 6, 9 and 11 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner says that claims contain subject matter which was not described in the specification. The Examiner states:

*Newly submitted claims introduce new matter in the claims because "the phrase "unconjugated Streptococcus pneumoniae protein" which is not disclosed, taught or supported in the instant specification. Applicant has failed to direct the Examiner as to where in the instant specification the support for this amendment is specifically shown or implied.*

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The broadest claim that is claim 1 relates to an immunologic composition comprising at least three elements, i.e. (1) at least one Streptococcus pneumoniae polysaccharide-protein conjugate, (2) least one unconjugated Streptococcus pneumoniae protein antigen, and (3) an adjuvant which is a preferential inducer of a TH1 response.

Attention is invited to Example 4 of page 47-51. In particular on page 47, lines 1-3 teaches

*Beneficial impact of the addition of pneumolysin and 3D-MPL on the protective effectiveness of PD-conjugated 11-valent polysaccharide vaccine against pneumococcal lung colonization in mice.*

Example 4 composition is in which a Streptococcus pneumoniae protein antigen (in this case pneumolysin) is unconjugated. Applicant offers apologies to the Examiner if Applicant has failed in the response to the last office action to direct the Examiner as to where exactly, such as by page numbers and lines, the support for the amendment can be found.

Applicant believes Applicant addressed all the issues brought up by the Examiner. Applicant further believes the case is now in condition for allowance. Re-consideration and re-examination are respectfully requested. If it would expedite the prosecution of this application, the Examiner is invited to confer with the undersigned attorney.

Respectfully submitted,



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